Convergent Synthesis of Vitamin D_3 Metabolites. Control of the Stereoselectivity in Samarium-Induced Cyclopropanations of Cyclopentenes

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The 25-hydroxy and 1α,25-dihydroxy vitamin D_3 metabolites are obtained by solvolytic rearrangements of the 1-desoxy and 1α-hydroxy cyclopropyl vinylogous alcohols **31** and **29**, respectively, with simultaneous formation of the vitamin D structural triene and the 3-hydroxy function. Two complementary methods have been employed to direct the stereoselectivity of the samarium induced olefin cyclopropanations which ultimately lead to key chiral ring A precursors. One protocol uses the two stereogenic centers of the (*R*,*R*)-2,3-butanediol ketal moiety of **8**, while the other method uses the allylic hydroxyl group of (*R*)-**16**.

The hormonally active metabolite of vitamin D_3, 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$, **1**), plays a major role in the maintenance of calcium and phosphorous homeostasis in the blood, and mineralization and calcium mobilization in the bones.[1] The widespread tissue distribution of specific nuclear receptors for 1,25-$(OH)_2D_3$ (VDR) and the participation of these receptors in the regulation of transcriptional processes in various cells significantly expands the scope of the hormonal activity of **1**.[2] These transcriptional activities of 1,25-$(OH)_2D_3$ have been implicated in the control of cellular proliferation and differentiation and may well form the basis of many of its physiological activities; however, more recently, a number of 1,25-$(OH)_2D_3$ activities have been recognized that do not involve binding to VDR. Instead, they appear to be initiated at the cellular membrane level by mechanisms which are not yet fully elucidated.[3] 1,25-$(OH)_2D_3$ was developed as a therapeutic agent for the treatment of diseases associated with renal failure, secondary hyperparathyroidism[4,5] and osteodystrophy,[6] post menopausal osteoporosis,[7−9] psoriasis,[10,11] and scleroderma.[12] Ongoing investigations with **1** and its numerous analogs have now focused on cancer and autoimmune diseases.

This compelling and robust progress in the pharmacology and medicine of 1,25-$(OH)_2D_3$ has stimulated efforts aimed at the development of efficient synthetic methodology that could be applied not only to the preparation of **1** but also to the synthesis of analogs, which, ideally, would have improved biological profiles. The original partial synthesis approach from steroidal precursors employing a photolytic opening of ring B[13] has been supplanted in time by totally synthetic procedures. Most of these are convergent approaches which involve the coupling of preformed C,D-side chain units with ring A units or precursors.[14] One of the synthetic approaches to **1** pursued in our laboratories was inspired by the early work of Mazur[15] and Wilson.[16] As illustrated in a retrosynthetic sense in Scheme 1, we have examined the solvolytic behavior of the vinylogous cyclopropyl alcohol **2**. It was anticipated that, under the solvolytic conditions, rearrangement of **2** would lead to intermediate cyclopropyl π-allyl cation **3**, which, on capture of water, would generate the 1α-hydroxy triene system in **1**.[17] In this report we describe, in detail, the results of this investigation which involves two asymmetric preparations of the acetylenic ring A precursors **4a**−**c** from 2-cyclopentenone (**5**) and which culminates in an efficient overall synthesis of **1**.

In contrast to our previous work on convergent approaches to vitamin D systems where the synthesis and

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(1) Walters, M. R. *Endocrine Rev.* **1992**, *13*, 719.
(2) Studzinski, G. P.; McLane, J. A.; Uskoković, M. R. *Crit. Rev. Eukaryotic Gene Expression* **1993**, *3*, 279.
(3) Norman, A. W.; Okamura, W. H.; Farach-Carson, M. C.; Allewaer, K; Branisteanu, D.; Nemere, I.; Muralidharan, K. R.; Bouillon, R. *J. Biol. Chem.* **1993**, *268*, 13811. Nemere, I.; Dormanen, M. C.; Hammond, M. W.; Okamura, W.; Norman. A. W. *J. Biol. Chem.* **1994**, *269*, 23750.
(4) Llach, F.; Massry, S. G. *J. Clin. Endocrinol. Metab.* **1985**, *61*, 601.
(5) Massry, S. G. *Metabolism* **1990**, *39*, 13.
(6) Healy, M.; Malluche, H. H.; Goldstein, D. S. *Arch. Intern. Med.* **1980,** *140*, 1030.
(7) Caniggia, A.; Nuti, R.; Lore, F.; Martini, G.; Turchetti, V.; Righi, G. *Metabolism* **1990**, *39*, 43.
(8) Gallagher, J. C.; Riggs, B. L. *Metabolism* **1990**, *39*, 30.
(9) Tilyard, M. W.; Spears, G. F. S.; Thomson, J.; Dovey, S. *New Eng. J. Med.* **1992**, *326*, 357.
(10) Smith, E. L.; Pincus, S. H.; Donovan, L.; Holick, M. F. *J. Am. Acad. Derm.* **1988**, *19*, 516.
(11) Langer, A.; Verjans, H.; Stapor, V.; Mol, M.; Fraczykowska, M. *Br. J. Derm.* **1993**, *128*, 566.
(12) Humbert, P.; Delaporte, E.; Dupond, J. L.; Rochefort, A.; Laurent, R.; Drobacheff, C.; DeWazieres, B.; Bergoend, H.; Agache, P. *Eur. J. Derm.* **1994**, *4*, 21.
(13) Semmler, E. J.; Holick, M. F.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1972,** *13*, 4147.
(14) (a) Lythgoe, B. *Chem. Soc. Rev.* **1981**, 449. (b) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskoković, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945. (c) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskoković, M. R. *J. Org. Chem.* **1986**, *51*, 3098. (d) Mascarenas, J. L.; Sarandeses, L. A.; Castedo, L.: Mourino, A. *Tetrahedron* **1991**, *47*, 3485. (e) Trost, B. M.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1924.
(15) Sheves, M.; Mazur, Y. *Tetrahedron Lett.* **1976**, *17*, 2987.
(16) Wilson, S. R.; Venkatesan, A. M.; Augelli-Szafran, C. E. *Proceedings of the Seventh Workshop on Vitamin D: Vitamin D Molecular, Cellular and Clinical Endocrinology*; de Gruyter: Berlin, 1988; p 43. Wilson, S. R.; Venkatesan, A. M.; Augelli-Szafran, C. E.; Yasmin, A. *Tetrahedron Lett.* **1991**, *32*, 2339.
(17) Preliminary communication: Kabat, M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1991**, *32*, 2343.
(18) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskoković, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945. Wovkulich, P. M.; Baggiolini, E. G.; Hennessy, B. M.; Uskoković, M. R.; Mayer, E.; Norman, A. W. *J. Org. Chem.* **1983**, *48*, 4433. Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B. M.; Uskoković, M. R. *Tetrahedron* **1984**, *40*, 2283. Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskoković, M. R. *J. Org. Chem.* **1986**, *51*, 3098. Baggiolini, E. G.; Hennessy, B. M.; Iacobelli, J. A.; Uskoković, M. R. *Tetrahedron Lett.* **1987**, *28*, 2095. Shiuey, S.; Kulesha, I.; Baggiolini, E. G.; Uskoković, M. R. *J. Org. Chem.* **1990**, *55*, 243. Kiegiel, J.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1991**, *32*, 6057. Kabat, M. M.; Lange, M.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 7701. Wovkulich, P. M.; Baggiolini, E. G.; Hennessy, B. M.; Uskoković, M. R. *Heterocycles* **1993**, *35*, 791. See also: Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383.

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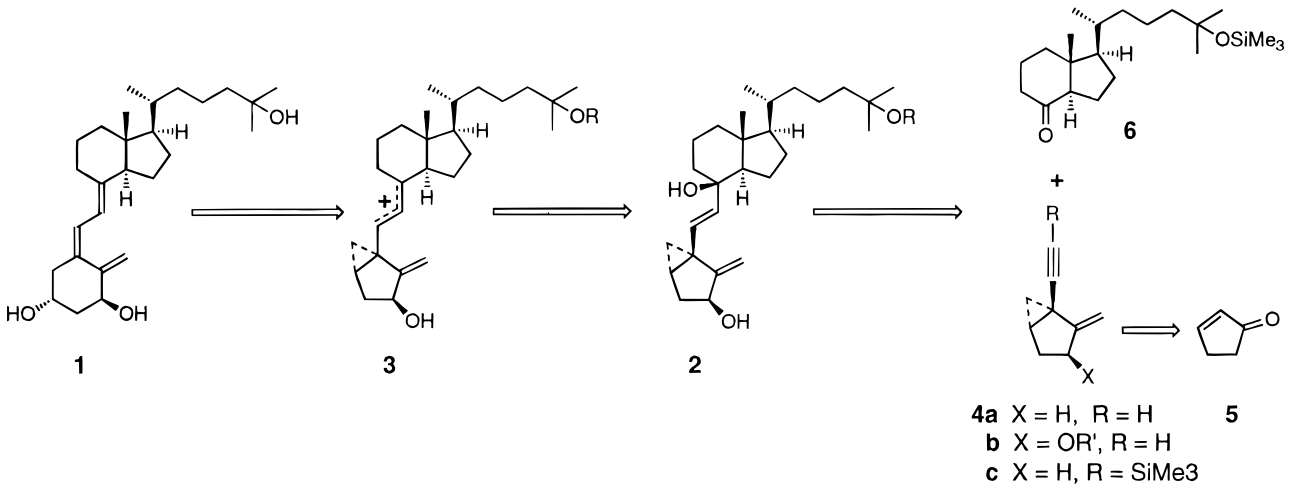
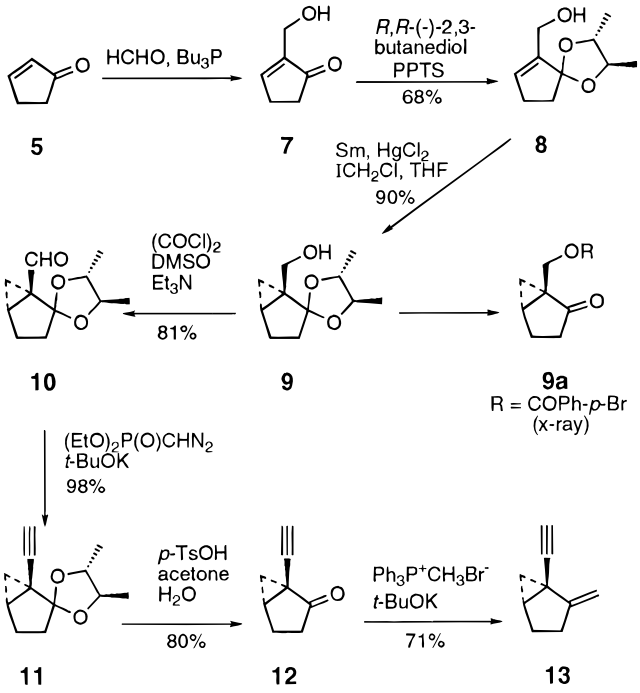
Scheme 1



use of preformed ring A units as six-membered rings was explored,[18] the present study addressed the use of ring A units in a latent form, as embodied in a suitably functionalized bicyclo[3.1.0]hexane. Since the solvolytic addition of water to the cyclopropyl system was expected to be stereospecific, it was essential to secure a facile preparation of the chiral bicyclo[3.1.0]hexane fragment possessing high enantiomeric and diastereomeric purities. We investigated two approaches, each of which involved the cyclopropanation of a substituted cyclopentene but differed by the elements utilized to influence the asymmetric cyclopropanation. Conveniently, both routes emanated from a common starting material, 2-cyclopentenone (**5**).

In the first approach, facial discrimination at the cyclopropanation step was envisioned as being directed by the two stereogenic centers present in an (*R*,*R*)-2,3-butanediol-derived ketal, following the precedent of Mash.[19] For this sequence, ketone **7**, obtained from 2-cyclopentenone (**5**) and formaldehyde,[20] was converted to the corresponding ketal **8** under acidic conditions with (*R*,*R*)-2,3-butanediol (Scheme 2). The diastereoselective cyclopropanation of ketal **8** using Zn(Cu)- or Et_2Zn-based methods was relatively inefficient, unlike the earlier examples of this reaction which were not complicated by the presence of free hydroxyl groups. However, application of the samarium-mediated cyclopropanation conditions described by Molander [ICH_2Cl, Sm(Hg)][21] provided a very clean reaction, generating the desired bicyclo[3.1.0]-hexane **9** in good yield and with greater than 20:1 diastereoselectivity.[22] At this stage, the absolute configuration of **9** was assigned on the basis of an X-ray analysis of the corresponding ketone **9a** obtained by *p*-bromobenzoylation of **9** followed by ketal hydrolysis.[23] The acetylenic portion of this ring A precursor was introduced by the reaction of aldehyde **10**, obtained uneventfully from **9** by Swern[24] oxidation, with diethyldiazomethyl phosphonate[25] to form acetylene **11**. Acidic

Scheme 2



hydrolysis of the ketal (**11** → **12**) and Wittig olefination completed the first construction of the ring A synthon **13**.

In the second approach to the ring A synthon, the cyclopropanation would also be directed by a temporarily situated stereogenic center, only this time it would exist in the form of a secondary allylic alcohol. For this sequence, cyclopentenone (**5**) was iodinated under our newly developed conditions to form 2-iodo-2-cyclopentenone (**14**).[26] Asymmetric reduction of **14** using the catalytic system described by Corey[27] and co-workers produced alcohol **15** in 82% yield and 92% ee (Scheme 3). Further improvement of the enantiomeric purity to 96% ee was achieved by recrystallization.[28] The acetylenic side chain

(19) (a) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679. (b) Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721.

(20) Wovkulich, P. M.; Kiegiel, J.; Uskoković, M. R. Manuscript in preparation. For an alternative preparation see: Smith, A. B.; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Org. Syn.* **1983**, *61*, 65.

(21) Molander, G. A.; Etter, J. F. *J. Org. Chem.* **1987**, *52*, 3942. Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525.

(22) The diastereoselectivity was 97:3 by capillary GC (50 M OV-17 column, 80−250 °C), which was also observed to be >95:5 by NMR.

(23) The keto *p*-bromobenzoate derivative **9a** has the [1(*S*)-*cis*] configuration, as shown: mp 65−66 °C, $[\alpha]^{25}_D = -20°$ (*c* 0.5, hexane).

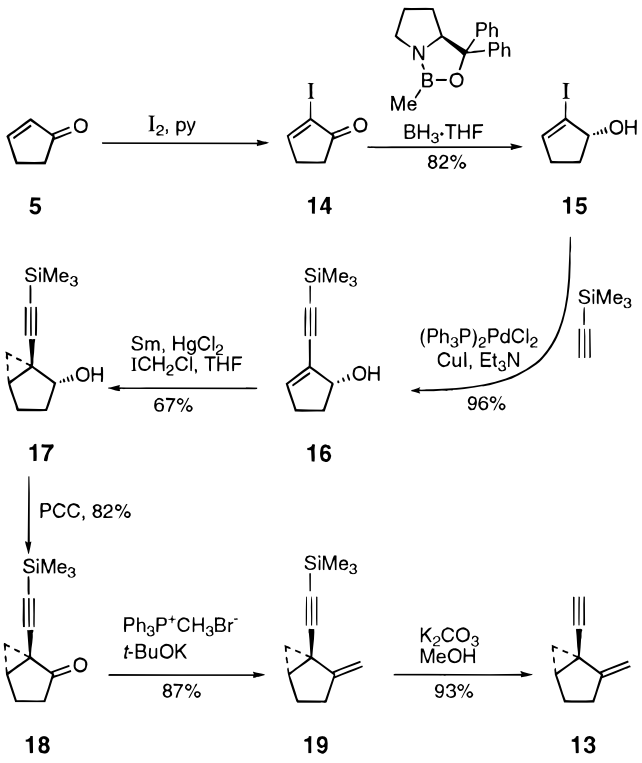
(24) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(25) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. Regitz, M.; Liedhegener, A.; Eckstein, U.; Martin, M.; Anschutz, W. *Ann.* **1971**, *748*, 207. Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.

(26) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.

(27) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

Scheme 3

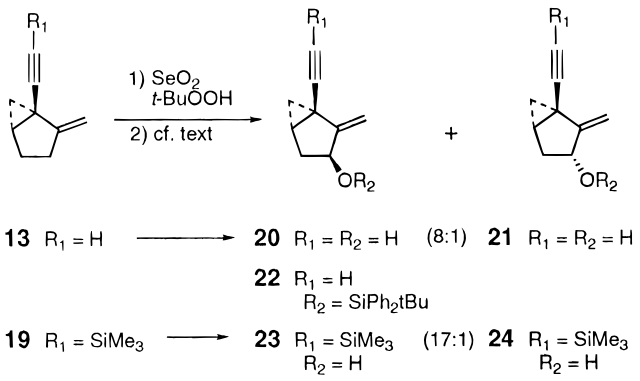


was then introduced by $(Ph_3P)_2PdCl_2-CuI$[29] -catalyzed coupling of the allylic (1*R*)-2-iodocyclopenten-1-ol (**15**) with (trimethylsilyl)acetylene.[30] As before, the cyclopropanation was best carried out under the Sm-mediated conditions, which proceeded in this case to give **17** in 67% yield. Wittig olefination of the corresponding ketone **18** gave the ring A precursor **19**, and further desilylation gave **13**, identical with the material prepared above.

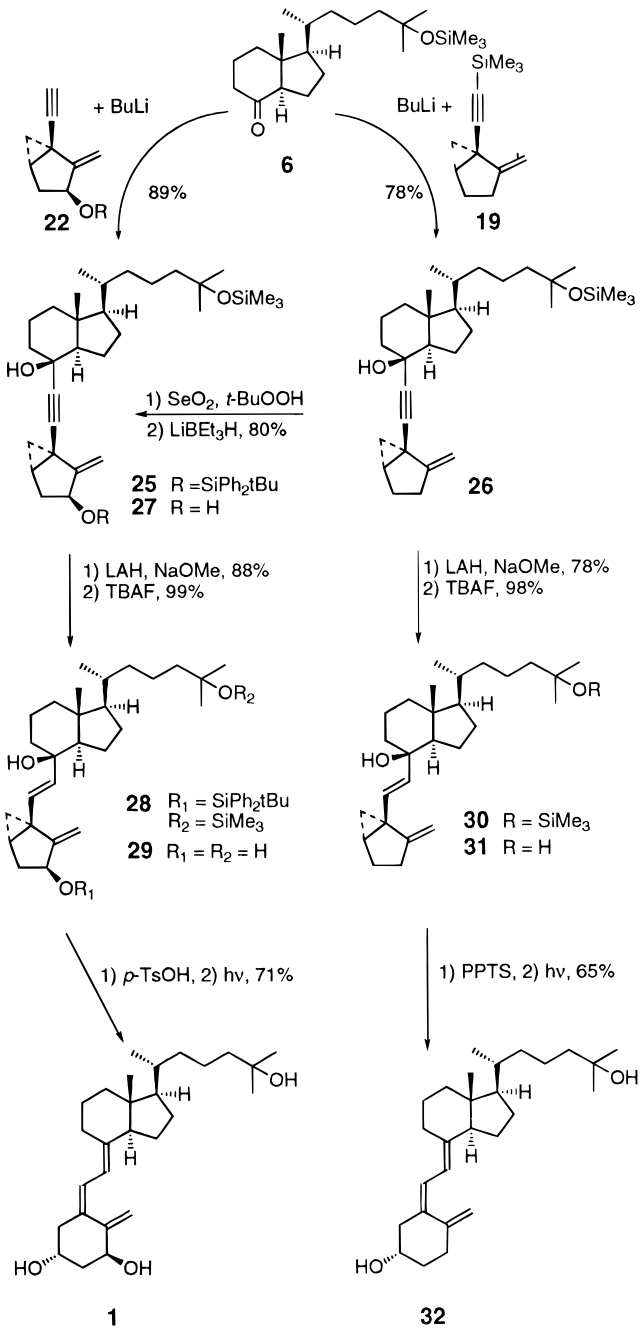
In terms of biological activity, a critical structural feature of 1,25-$(OH)_2D_3$ is the presence of the 1α-hydroxy group. To introduce this functionality into our bicyclo[3.1.0]hexane precursor units, we first investigated the allylic hydroxylation of compounds **13** and **19**. Treatment of **13** with an excess of *t*-BuOOH in the presence of a catalytic amount of SeO_2 afforded a mixture of allylic alcohols **20** and **21** in an 8:1 ratio in 54% yield (Scheme 4). The stereochemistry of **20** was established by an X-ray crystallographic analysis of the corresponding *tert*-butyldiphenylsilyl derivative **22**. An improvement on this hydroxylation scheme was realized in the oxidation of the C-silylated acetylene **19**, which could be smoothly oxidized all the way to the corresponding ketone. Without isolation, the intermediate ketone was then reduced with lithium triethylborohydride to give allylic alcohols **23** and **24** as a 19:1 mixture in 75% overall yield.

With the preparation of the ring A units in hand, we next turned our attention to the attachment of these synthons to the CD fragments, focusing our efforts first on the coupling reactions with **22**. The acetylide anion of **22**, formed in THF with an equimolar amount of *n*-butyllithium, reacted with 25-trimethylsilyloxy Windaus–Grundman ketone **6**[31] to produce the propargylic alcohol **25** as a single diastereomer in 89% yield (Scheme 5).[17] We next investigated an alternative preparation of this key intermediate using the nonhydroxylated ring A precursor **19**. In addition to the preparation of **25**, this second approach also provides access to the

Scheme 4



Scheme 5



(28) The ee was measured by NMR of the corresponding MTPA esters. The methoxy group was diagnostic for this measurement at 3.67 ppm for the *RR* ester and at 3.57 ppm for the *RS* ester.

(29) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

(30) In contrast, when the order of events was reversed, i.e., acetylenic coupling with iodo enone **14** first, followed by the asymmetric reduction, the enantiomeric purity of the product alcohol **16** was lower (70% ee).

synthesis of 25-hydroxy vitamin D_3 (**32**), another metabolite of vitamin D_3. It is noteworthy that in this instance the C−Si bond cleavage may be carried out *in situ* by the treatment of the silylated acetylene **19** with an equimolar amount of *n*-butyllithium, to give the corresponding acetylide anion which on reaction with **6** formed the corresponding nonhydroxylated propargylic alcohol **26** in 78% yield. Application of the same hydroxylating conditions used for the **19** to **23** conversion (excess *t*-BuOOH, catalytic SeO_2, followed by $LiEt_3BH$ reduction) produced the 1α-hydroxy epimer **27** as a single isomer. Selective protection of the secondary hydroxyl group with *t*-$BuPh_2SiCl$ gave **25** (88% yield), which was identical by analytical and spectral comparisons with the material derived from **22**.

The final phase of this synthetic strategy comprised a solvolytic opening of the bicyclo[3.1.0]hexane system, which would generate the triene system with concomittant introduction of the required 3β hydroxyl group of vitamin D. For this operation the propargylic alcohol portion of **25** was reduced stereoselectively to *trans*-allylic alcohol **28** (88% yield) using $LiAlH_4$ in the presence of sodium methoxide. The silyl groups of **28** were then removed (Bu_4NF) to form the free hydroxy derivative **29**. The solvolysis of **29** was carried out with *p*-toluenesulfonic acid in dioxane−water at 75 °C to produce, in 75% yield, a 7:3 mixture of 1,25-$(OH)_2D_3$ (**1**) and its 5,6-*trans* diastereomer. The undesired *trans* compound was isomerized by photolysis of the mixture in the presence of 9-acetoxyanthracene using a 450 W mercury lamp equipped with a uranium filter. In this manner the desired isomer **1** was obtained in 95% yield, which was analytically and spectroscopically identical to authentic material.[14c]

In a similar fashion, intermediate **31**, the compound lacking the 1α-hydroxyl group, was correspondingly transformed to 25-OH vitamin D_3 (**32**). As in the previous case, reduction of the propargylic alcohol in **26** to the *trans* allylic alcohol was conducted with $LiAlH_4$−NaOMe to give **30** in 78% yield. After removal of the silyl ether, the resulting diol **31** underwent solvolytic rearrangement (pyridinium *p*-toluenesulfonate, CH_3CN-H_2O, 50 °C) to a mixture of 25-(OH)-D_3 (**32**) and its 5,6 *trans* isomer. Subsequent photoisomerization of the mixture gave **32** in 65% overall yield.

In summary, we have demonstrated the utility of the solvolysis of vinylogous cyclopropyl alcohols for the sterespecific introduction of the C3 hydroxyl group along with the simultaneous generation of the vitamin D triene system, a bond reorganization process reminiscent of the classical i-steroid rearrangement. Two practical routes to the key chiral bicyclo[3.1.0]hexane intermediates **19** and **22** were devised, each involving different cyclopropanations of substituted cyclopentenes and both starting from 2-cyclopentenone.

Experimental Section

General. Materials and Methods. Melting points were measured in open capillary tubes and are uncorrected. ^1H NMR spectra were obtained in $CDCl_3$ at 400 MHz. Unless otherwise noted, reactions were conducted under an atmosphere of dry argon. Organic extracts mixtures were dried over anhydrous Na_2SO_4 or $MgSO_4$, and filtered, and the solvent was then removed under reduced pressure. Chromatography was performed on 230−400 mesh EM silica gel 60.

(2*R*,3*R*)-(−)-2,3-Dimethyl-1,4-dioxaspiro[4.4]non-6-ene-6-methanol (8). A solution of 20.0 g (0.18 mol) of hydroxy ketone **7**,[20] 32.1 g (0.36 mol) of *(2R,3R)*-(−)-butanediol, 0.55 g (2.2 mmol) of pyridinium *p*-toluenesulfonate, and 1.5 L of CCl_4 was heated at reflux for 8 h with azeotropic removal of water. The mixture was cooled to rt, 2 mL of pyridine was added, and the solution was filtered through silica gel (400 g). The filtrate was concentrated *in vacuo*. Chromatography of the crude product on silica gel, eluting with hexane−EtOAc (85:15), gave 22.3 g (68%) of ketal **8** as a colorless oil: $[\alpha]^{25}_D = -3.2°$ (*c* 1, EtOH); IR ($CHCl_3$) 3533 cm^{-1}; ^1H NMR δ 1.27 (d, J = 6 Hz, 3H), 1.30 (d, J = 6 Hz, 3H), 2.13 (m, 2H), 2.37 (m, 2H), 3.68 (m, 2H), 4.25 (d, J = 3.8 Hz, 2H), 6.03 (s, 1H); MS (*m/z*) 184 (M^+, 25), 169 (M − Me, 20), 167 (M − OH, 18), 155 (36), 140 (8), 129 (16), 111 (100), 95 (36), 83 (35), 67 (45), 55 (53); HRMS for $C_{10}H_{16}O_3$ calcd 184.1099, found 184.1105. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.99; H, 8.72.

[4′*R*,5′*R*-(1*S*-*cis*)]-(+)-4′,5′-Dimethylspiro[bicyclo[3.1.0]-hexane-2,2′-[1,3]dioxolane]-1-methanol (9). The procedure of Molander[21] was employed. A 500 mL, three-necked flask fitted with a magnetic stirrer, reflux condenser, rubber septum, and thermometer was charged with 15.0 g (0.1 g-atom of 35 mesh, Rhone-Poulenc) of samarium powder. The metal and apparatus were cautiously flame dried after thorough evacuation of air and introduction of argon. The metal was stirred during deaeration and drying steps to insure the elimination of air pockets. After being cooled to rt, the metal was covered with 500 mL of anhydrous THF and a solution of 2.6 g (9.57 mmol) of $HgCl_2$ in 30 mL of dry THF was added with stirring, followed by the addition of a solution of 4.15 g (22.5 mmol) of hydroxy ketal **8** in 25 mL of dry THF. The mixture was stirred and cooled to −73 °C (dry ice−acetone bath), and 16.8 g (92.35 mmol) of ICH_2Cl was added dropwise via syringe. After being stirred at −73 °C for 20 min, the reaction mixture was allowed to warm spontaneously by removal of the cooling bath, but the internal temperature was kept below 40 °C by occasional immersion in an ice bath. When the temperature fell to 24 °C, the reaction mixture was warmed in a hot water bath to 40 °C for 30 min. The total reaction time at 24−37 °C was 2 h. A saturated aqueous K_2CO_3 solution was then added, and workup was carried out by extraction with ether. The crude product (5.0 g) was chromatographed on silica gel, eluting with hexane−EtOAc (2:1), to give 4.05 g (90%) of cyclopropane alcohol **9** as a colorless liquid: $[\alpha]^{25}_D = +32.6°$ (*c* 1, EtOH); ^1H NMR δ 0.58 (dd, J = 5.2, 7.8 Hz, 1H), 0.77 (t, J = 0.9 Hz, 1H), 1.24 (d, J = 6.0 Hz, 3H), 1.34 (d, J = 6.0 Hz, 3H), 1.45−1.65 (m, 3H), 1.72 (dd, J = 8.6, 12.7 Hz, 1H), 1.85−1.98 (m, 1H), 2.77 (dd, J = 0.8, 9.6 Hz, 1H), 3.34 (dd, J = 9.6, 12 Hz, 1H), 3.60 (m, 1H), 3.77 (m, 1H), 4.07 (d, J = 12.0 Hz, 2H); MS (*m/z*) 198 (M^+, 25), 181 (M − OH, 46), 169 (39), 155 (64), 143 (17), 127 (52), 114 (100), 95 (30), 85 (64), 55 (98); HRMS for $C_{11}H_{18}O_3$ calcd 198.1256, found 198.1244. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.46; H, 9.18.

[4′*R*-[2′α(1*S,5*R**),4′α,5*β*]]-4′,5′-Dimethylspiro[bicyclo-[3.1.0]hexane-2,2′-[1,3]dioxolane]-1-carboxaldehyde (10).** A solution of 17.6 mL (240 mmol) of DMSO in 30 mL of CH_2Cl_2 was added slowly to a cold solution (−60 °C) of 10.84 mL (120 mmol) of oxalyl chloride in 200 mL of CH_2Cl_2. The resulting mixture was stirred at −60 °C for 15 min, and then 8.2 g (40 mmol) of alcohol **9** in 20 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to warm to −20 °C over 30 min, cooled again to −60 °C and then treated with 35.6 mL (240 mmol) of triethylamine. The cooling bath was then removed, and stirring was continued at rt for 1 h. The solution was washed with water and dried. The crude product was chromatographed on a silica gel, eluting with hexane−ether (9:1), to give 6.59 g (81%) of aldehyde **10**, as a slightly yellow oil: $[\alpha]^{25}_D = -46.8°$ (*c* 0.95, EtOH); IR ($CHCl_3$) 1752, 1700 cm^{-1}; ^1H NMR δ 1.26 (d, J = 6.0 Hz, 3H), 1.36 (d, J = 6.0 Hz, 3H), 1.5−1.85 (m, 4H), 1.85−2.05 (m, 1H), 2.05−2.15 (m, 1H), 3.65−3.75 (m, 1H), 3.75−3.85 (m, 1H), 10.00 (s, 1H); MS (*m/z*) 196 (M^+, 19), 179 (M − OH, 10), 167 (95), 114 (80), 96 (61), 83 (100); HRMS for $C_{11}H_{16}O_3$ calcd 196.1099, found 196.1087.

[4′*R*,5′*R*-(1*S*-*cis*)]-1-Ethynyl-4′,5′-dimethylspiro[bicyclo-[3.1.0]hexene-2,2′-[1,3]dioxolane (11). A suspension of 6.03 g (5.4 mmol) of *t*-BuOK in 200 mL of THF at −70 °C was treated with a solution of 8.98 g (5.0 mmol) of $(EtO)_2P(O)CHN_2$[25] in 20 mL of THF. The mixture was stirred for 15 min, and then a solution of 6.59 g (3.3 mmol) of aldehyde **10** in 30 mL of THF was added dropwise. Stirring was continued

(31) Kiegiel, J.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1991**, *32*, 6057. See also ref 14b,c.

for 30 min, and then the temperature was allowed to rise to rt. Then 500 mL of H_2O was added, and the solution was extracted with ether. The extracts were combined and washed three times with water and dried. The crude product was chromatographed on silica gel, eluting with hexane−ether (97:3), to give 6.35 g (98%) of acetylene **11** as a colorless oil: $[\alpha]^{25}_D = -49.6°$ (*c* 1.19, EtOH); IR ($CHCl_3$) 3310, 2115 cm^{-1}; ^1H NMR δ 1.03 (m, 2H), 1.23 (d, $J = 3.9$ Hz, 3H), 1.38 (d, $J = 4.0$ Hz, 3H), 1.5−1.7 (m, 2H), 1.82 (m, 1H), 2.01 (s, 1H), 3.55−3.62 (m, 1H), 3.97−4.05 (m, 1H); MS (*m*/*z*) 192 (M^+, 23), 177 (M − 15, 2), 120 (71), 144 (100), 91 (69); HRMS for $C_{21}H_{16}O_2$ calcd 192.1152, found 192.1150. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.76; H, 8.55.

(1*S*-*cis*)-1-Ethynylbicyclo[3.1.0]hexan-2-one (12). A solution of 6.90 g (3.6 mmol) of ketal **11**, 0.07 g of *p*-TsOH, 50 mL of acetone, and 10 mL of H_2O was refluxed for 2 d. The acetone was evaporated *in vacuo*, and the residue was extracted with ether. The organic phase was washed successively with water and an aqueous $NaHCO_3$ solution and dried. The crude product was purified by chromatography on silica gel, eluting with hexane−ether (85:15), to give 3.45 g (80%) of ketone **12** as a colorless oil: $[\alpha]^{25}_D = -78.3°$ (*c* 1.1, EtOH); IR ($CHCl_3$) 3315, 2125, 1695 cm^{-1}; ^1H NMR δ 1.44 (t, $J = 5.1$ Hz, 1H), 1.64 (m, 1H), 1.95−2.05 (m, 1H), 2.15−2.30 (m, 3H), 2.18 (s, 1H), 2.45−2.55 (m, 1H); MS (*m*/*z*) 120 (M^+, 8), 105 (M − 15, 5), 91 (70), 79 (34), 63 (45, 51 (100), 39 (78); HRMS for C_8H_8O calcd 120.0575, found 120.0573. Anal. Calcd for C_8H_8O: C, 79.97; H, 6.71. Found: C, 79.60; H, 6.71.

(1*S*-*cis*)-1-Ethynyl-2-methylenebicyclo[3.1.0]hexane (13). A suspension of 14.22 g (39.8 mmol) of methyltriphenylphosphonium bromide and 4.46 g (39.8 mmol) of *t*-BuOK in 100 mL of THF was stirred under argon, at rt for 30 min. To the above mixture, a solution of 2.39 g (19.9 mmol) of ketone **12** in 10 mL of THF was added. After stirring for 1 h, 200 mL of H_2O was added and the solution was extracted with pentane. The pentane layer was washed with 8 × 100 mL of H_2O and then dried. The solution was passed through a short pad of silica gel (300 g) eluting with pentane-ether (9:1). Fractional distillation at atmospheric pressure of the combined fractions containing the product afforded 1.66 g (71%) of olefin **13**, bp 153−155 °C: $[\alpha]^{25}_D = -46.2°$ (*c* 1.1, EtOH); IR ($CHCl_3$) 3305, 2115, 1657 cm^{-1}; ^1H NMR δ 1.03 (t, $J = 4.8$ Hz, 1H), 1.23 (dd, $J = 4.4$, 7.7 Hz, 1H), 1.60−1.70 (1H, m), 1.90−2.05 (m, 2H), 2.14 (s, 1H), 2.20−2.30 (m, 1H), 4.90 (s, 1H), 5.17 (d, $J = 0.9$ Hz, 1H); MS (*m*/*z*) 118 (M^+, 32), 117 (M − 1, 100), 115 (M − 2H, 50), 103 (M − Me, 61). HRMS for C_9H_{10} 118.0783 calcd, found 118.0781. Anal. Calcd for C_9H_{10}: C, 91.47; H, 8.53. Found: C, 91.06; H, 8.59.

(*R*)-2-Iodo-2-cyclopenten-1-ol (15). To a solution of 3.639 g (13.13 mmol) of *(S)*-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazaborole[27] in 260 mL of THF at 0 °C were added simultaneously over 0.5 h solutions of 27.30 g (131 mmol) of 2-iodo-2-cyclopentenone **14**[26] in 80 mL of THF and 78.8 mL (78.8 mmol) of 1.0 M BH_3·THF in THF. The reaction mixture was stirred at 5 °C for 30 min, after which 60 mL of aqueous buffer (pH = 7) was added, followed by 20 mL of 30% H_2O_2. After being stirred for 20 min, 400 mL of EtOAc was added and the solution was washed successively with 200 mL of 1 N HCl, 200 mL of H_2O, 200 mL of saturated $NaHCO_3$, and 200 mL of brine and then dried. The product was crystallized from ether−pentane to give 23.16 g (84%) of **15** as colorless crystals, mp 61.3−61.7 °C; The ^1H NMR of the Mosher ester of **15** ((*R*)-acid) showed 92% ee for crude product and 96% ee after crystallization: $[\alpha]^{25}_D = +16°$ (*c* 1.1, EtOH); IR ($CHCl_3$) 3590, 1600 cm^{-1}; ^1H NMR δ 1.81−1.90 (m, 1H), 2.26−2.38 (m, 2H), 2.45−2.54 (m, 1H), 4.69 (brs, 1H), 6.29 (t, $J = 2.4$ Hz, 1H); MS (*m*/*z*) 210 (M^+, 25), 83 (100). Anal. Calcd for C_5H_7IO: C, 28.60; H, 3.36. Found: C, 28.94; H, 3.38.

(*R*)-2-[(Trimethylsilyl)ethynyl]-2-cyclopenten-1-ol (16). To a solution of 21.50 g (102.4 mmol) of **15** in 250 mL of dry benzene was added 28.52 mL (204.6 mmol) Et_3N at rt and the reaction flask was flushed with argon. Then 32.5 g (330.9 mmol) of trimethylsilylacetylene was added followed by 0.359 g (0.515 mmol) of $(Ph_3P)_2PdCl_2$ and 0.294 g (1.545 mmol) of CuI. An exothermic reaction occurred and the temperature rose to *ca* 40 °C. After stirring for 20 min, the reaction mixture was diluted with 300 mL of EtOAc and the organic solution was washed successively with 200 mL of 0.5 N H_2SO_4, 200 mL of H_2O, 200 mL of saturated aqueous $NaHCO_3$, and 100 mL of brine. The washes were back extracted and the combined organic layers were dried. The residue was distilled bulb to bulb (oven 85-105 °C, 2 mm Hg) to afford 17.74 g (96%) of **16** as colorless, low melting crystals. An analytical sample was obtained by chromatography on silica gel eluting with hexane-EtOAc (4:1): $[\alpha]^{25}_D = -7.2°$ (*c* 0.9, EtOH); IR ($CHCl_3$) 3590, 2145 cm^{-1}; ^1H NMR δ 0.21 (s, 9H), 1.73−1.80 (m, 1H), 2.25−2.41 (m, 2H), 2.50−2.61 (m, 1H), 4.79 (brs, 1H), 6.27 (t, $J = 2.7$ Hz, 1H); MS (*m*/*z*) 180 (M^+, 18), 165 (23), 99 (100). Anal. Calcd for $C_{10}H_{16}OSi$: C, 66.61; H, 8.94. Found: C, 66.80; H, 8.84.

[*S*-(1α,2*β*,5α)-1-[(Trimethylsilyl)ethynyl]bicyclo[3.1.0]-hexan-2-ol (17). A 500 mL, three-necked, round bottom flask was charged with 58.37 g (388 mmol) of samarium metal powder (obtained from Rhone-Poulenc Inc.). The metal and apparatus were cautiously flame dried after thorough evacuation of air and introduction of argon. The metal was stirred during deaeration and drying steps to insure the elimination of air pockets. After cooling to rt, 250 mL of THF was added followed by 2.635 g (9.7 mmol) of $HgCl_2$ in 10 mL of THF and 7.0 g (38.8 mmol) of alcohol **16** in 20 mL of THF. This mixture was cooled to −60 °C, and 2.55 mL (35 mmol) of ICH_2Cl was added. The mixture was then heated to 17 °C whereupon an exothermic reaction started. The further addition of 23.0 mL (314 mmol) of ICH_2Cl was continued at such a rate so as to maintain the temperature in the range 31−40 °C (cooled if neccessary with an acetone-dry ice bath). When the addition was complete and the exothermic reaction concluded, the mixture was cooled to 0 °C and then 75 mL of saturated aqueous K_2CO_3 was added portionwise (exothermic). Then 250 mL of H_2O was added, and the mixture was extracted with ether. The crude product was purified by silica gel chromatography, eluting with hexane−EtOAc (4:1), to give 5.054 g (67%) of **17** as colorless, low-melting crystals: $[\alpha]^{25}_D = -131.1°$ (*c* 1, EtOH); IR ($CHCl_3$) 3605, 2155 cm^{-1}; ^1H NMR δ 0.15 (s, 9H), 0.87−0.90 (m, 1H), 1.11−1.18 (m, 2H), 1.67−1.72 (m, 2H), 1.84−1.95 (m, 3H), 4.56 (brt, $J = 8.2$ Hz, 1H); MS (*m*/*z*) 194 (M^+, 2), 161 (21), 99 (35), 75 (100). Anal. Calcd for $C_{11}H_{18}OSi$: C, 67.98; H, 9.34. Found: C, 67.39; H, 9.57.

(1*S*-*cis*)-1-[(Trimethylsilyl)ethynyl]bicyclo[3.1.0]hexan-2-one (18). Pyridinium chlorochromate (10.43 g, 484 mmol) of was added to a solution of 4.70 g (24.2 mmol) of **17** in 250 mL of CH_2Cl_2. The slurry was stirred at rt for 3 h. The brown solution was decanted from the gummy dark solid, washed successively with 200 mL of saturated $NaHCO_3$ and 200 mL H_2O, and then dried. The crude product was purified by silica gel chromatography, eluting with hexane-EtOAc (10:1), to give 3.81 g (82%) of **18** as colorless crystals, mp 47−48.5 ° $[\alpha]^{25}_D = -70.6°$ (*c* 1.2, EtOH); IR ($CHCl_3$) 2165, 1728 cm^{-1}; ^1H NMR δ 0.16 (s, 9H), 1.41 (t, $J = 5.0$ Hz, 1H), 1.63−1.66 (m, 1H), 1.94−2.00 (m, 1H), 2.12−2.27 (m, 3H), 2.45−2.51 (m, 1H); MS (*m*/*z*) 192 (M^+, 3), 177 (100). Anal. Calcd for $C_{11}H_{16}OSi$: C, 68.69; H, 8.39. Found: C, 68.45; H, 8.37.

(1*R*-*cis*)-Trimethyl[(2-methylenebicyclo[3.1.0]hexyl)-ethynyl]silane (19). To a slurry of 78.09 g (219 mmol) of methyltriphenylphosphonium bromide in 1.2 L of THF at rt was added 26.77 g (219 mmol) of *t*-BuOK. The resulting mixture was stirred for 2 h, and then a solution of 21.02 g (109 mmol) of ketone **18** in 100 mL of THF was added over 15 min. After the mixture was stirred for an additional 30 min, 1 L of H_2O was added and the mixture was extracted with hexane. The organic layers were combined, dried, and concentrated under reduced pressure. The residue was dissolved in hexane, and the solution was filtered through silica gel (2 cm layer) eluting with hexane. The hexane was evaporated under reduced pressure. The residue was distilled (bp 71−76 °C at 2 mmHg) to afford 18.1 g (87%) of **19** as a colorless oil: $[\alpha]^{25}_D = -70.2°$ (*c* 0.9, EtOH); IR ($CHCl_3$) 3305, 2115, 1650 cm^{-1}; ^1H NMR δ 0.17 (s, 9H), 1.04 (t, $J = 4.7$ Hz, 1H), 1.23−1.28 (m, 1H), 1.69−1.76 (m, 1H), 1.90−2.07 (m, 3H), 2.19−2.27 (m, 1H), 4.90 (s, 1H), 5.16 (s, 1H); MS (*m*/*z*) 190 (M^+, 22), 175 (100). Anal. Calcd for $C_{12}H_{18}Si$: C, 75.71; H, 9.53. Found: C, 75.05; H, 9.38.

(1*S*-*cis*)-1-Ethynyl-2-methylenebicyclo[3.1.0]hexane (13). A mixture of 0.7 g (3.68 mmol) of compound **19**, 0.39 g (3.68 mmol) of Na_2CO_3 and 20 mL of MeOH was stirred at rt for 3.5 h. Then 10 mL of H_2O was added, and the mixture was extracted (3 × 10 mL) with pentane. The extracts were combined and dried. Solvents were removed under atmo-

spheric pressure by distillation using a 10 cm Vigreux column. The residue was distilled to afford 0.404 g (93%) of **13**, bp 153 °C. The analytical and spectral properties of the material prepared in this way were in full accord with those of compound **13** obtained via Scheme 2.

SeO_2 Oxidation of 13. A suspension of 0.468 g (4.22 mmol) of SeO_2, 14.07 mL of a 3 M solution of *t*-BuOOH in 2,2,4-trimethylpentane (42.21 mmol), and 40 mL of CH_2Cl_2 was stirred at rt for 30 min and then cooled to 0 °C. **13** (1.66 g, 14.07 mmol) in 5 mL of CH_2Cl_2 was added slowly. The reaction mixture was stirred at 0 °C for 2 h and then at rt for 4 h before being washed with water and dried. The crude product was chromatographed on silica gel, eluting with hexane−ether (92:8), to give 0.110 g (6%) of [1*S*-(1α,3*β*,5α)]-1-ethynyl-2-methylenebicyclo[3.1.0]hexan-3-ol (**21**) as a solid, mp 32−34 °C: $[\alpha]^{25}_D = -162.7°$ (*c* 1.05, EtOH); IR ($CHCl_3$) 3605, 3305, 2115, 1660, 1650 cm^{-1}; ^1H NMR δ 1.38 (m, 1H), 1.54 (t, $J = 4.7$ Hz, 1H), 1.81 (d, $J = 14.2$ Hz, 1H), 2.09 (m, 1H), 2.15 (s, 1H), 2.25 (m, 1H), 4.53 (d, $J = 6.2$ Hz, 1H), 5.23 (s, 1H), 5.39 (s, 1H); MS (*m*/*z*) 133 (M − H, 12), 115 (100), 105 (32), 91 (82), 77 (59); HRMS for C_9H_9O (M − H) calcd 133.0653, found 133.0654.

Further elution with hexane−ether (9:1) gave 0.905 g (48%) of the desired [1*S*-(1α,3α,5α)]-1-ethynyl-2-methylenebicyclo-[3.1.0]hexan-3-ol (**20**), also as a low melting solid, mp 38−39 °C: $[\alpha]^{25}_D = +18.8°$ (*c* 0.96, EtOH); IR ($CHCl_3$) 3620, 3585, 3305, 2115, 1645 cm^{-1}; ^1H NMR δ 0.93 (t, $J = 5.1$ Hz, 1H), 1.24 (dd, $J = 5.1$, 8.5 Hz, 1H), 1.6−1.7 (m, 1H), 1.96 (m, 1H), 2.19 (s, 1H), 2.34 (dd, $J = 7.6$, 12.6 Hz, 1H), 4.17 (brs, 1H), 5.20 (d, $J = 2.1$ Hz, 1H), 5.37 (d, $J = 2.5$ Hz, 1H); MS (*m*/*z*) 133 (M − H, 10%), 115 (M-18, 100), 105 (25), 91 (60), 77 (42), 63 (40), 51 (31), 39 (55). HRMS for C_9H_9O (M-H) calcd 133.0653, found 133.0642. Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.29; H, 7.59.

[1*S*-(1α,3α,5α)]-(1,1-Dimethylethyl)[(1-ethynyl-2-methylenebicyclo[3.1.0]hexan-3-yl)oxy]diphenylsilane (22). A solution of 0.710 g (5.30 mmol) of alcohol **20**, 1.21 mL (6.89 mmol) of *t*-$BuPh_2SiCl$, 0.469 g (6.89 mmol) of imidazole, and 10 mL of DMF was stirred at rt for 4 h. Water was then added, and the mixture was extracted with hexane. The extracts were combined, washed with water, and dried. The crude product was purified by silica gel chromatography, eluting with hexane−ether (97:3), to give 1.85 g (94%) of silyl ether **22**, mp 62−64 °C (MeOH). $[\alpha]^{25}_D = -71.8°$ (*c* 1.1, EtOH); UV λ_{max} (EtOH) 218 (ϵ = 19 500), 253 (430), 259 (635), 264 (695), 270 (530); IR ($CHCl_3$) 3305, 2115, 1660, 821, 702 cm^{-1}; ^1H NMR δ 0.75 (t, $J = 4.8$ Hz, 1H), 1.54 (s, 10 H), 1.7−1.9 (m, 3H), 2.15 (s, 1H), 4.21 (t, $J = 4.8$ Hz, 1H), 5.36 (s, 2H), 7.3−7.45 (m, 6H), 7.6−7.7 (m, 4H); MS (*m*/*z*) 372 (M^+, 1), 357 (M − 15, 1), 315 (M − C_4H_9, 65), 237 (50), 199 (100); HRMS for $C_{25}H_{28}OSi$ calcd 372.1909, found 372.1901. Anal. Calcd for $C_{25}H_{28}OSi$: C, 80.59; H, 7.58. Found: C, 80.77; H, 7.76.

Hydroxylation of Olefin 19: Preparation of [1*R*-(1α,3*β*,5α)]-2-Methylene-1-[(trimethylsilyl)ethynyl]bicyclo-[3.1.0]hexan-3-ol (24). A total of 2.625 mL of a 3.0 M *t*-BuOOH in 2,2,4-trimethylpentane (7.88 mmol) solution was added to a stirred slurry of 0.0875 g (0.788 mmol) SeO_2 in 15 mL of dry CH_2Cl_2, and the resulting mixture stirred at rt for 2 h. The reaction mixture was then cooled to 0 °C and treated with a solution of 0.5 g (2.627 mmol) of **19** in 5 mL of CH_2Cl_2. The reaction mixture was kept at 4 °C for 22 h whereupon 20 mL of 20% aqueous $Na_2S_2O_3$ was added and the mixture stirred for 30 min. The phases were separated, and the aqueous solution was extracted with ether. The organic solutions were combined, dried, and concentrated *in vacuo*. The residue was dissolved in 25 mL of dry THF and cooled to −50 °C, and 3.15 mL (3.15 mmol) of lithium triethylborohydride (1.0 M in THF) was added. The reaction mixture was allowed to warm to rt. Then 20 mL of H_2O was added, and the mixture was extracted with ether (2 × 20 mL). The extracts were combined, dried, and concentrated. The residue was chromatographed on silica gel, eluting with hexane−EtOAc (4:1), to give 0.408 g (75%) of **[1*R*-(1α,3α,5α)]-2-methylene-1-[(trimethylsilyl)ethynyl]bicyclo[3.1.0]hexan-3-ol (23)**, mp 74−79 °C (ether-hexane) $[\alpha]^{25}_D = -10.4°$ (*c* 1.0, EtOH); IR ($CHCl_3$) 3585, 2160, 1655 cm^{-1}; ^1H NMR δ 0.17 (s, 9H), 0.92 (t, $J = 4.9$ Hz, 1H), 1.22−1.26 (m, 1H), 1.72−1.78 (m, 1H), 1.93−1.99 (m, 1H), 2.30−2.35 (m, 1H), 4.16 (m, 1H), 5.18 (d, $J = 2.0$ Hz, 1H), 5.34 (d, $J = 2.5$ Hz, 1H); MS (*m*/*z*) 188 (M − 18, 14), 173 (100), 145 (21), 73 (80). Anal. Calcd for $C_{12}H_{18}OSi$: C, 69.84; H, 8.79. Found: C, 70.06; H, 8.77.] and 0.024 g (4%) of **[1*R*-(1α,3*β*,5α)]-2-methylene-1-[(trimethylsilyl) ethynyl] bicyclo[3.1.0] hexan-3-ol (24)**, as a low melting solid $[\alpha]^{25}_D = -158.1°$ (*c* 1.0, EtOH); IR ($CHCl_3$) 3605, 2160, 1650 cm^{-1}. ^1H NMR δ 0.17 (s, 9H), 1.36−1.39 (m, 1H), 1.53−1.56 (m, 1H), 1.79 (d, $J = 14.1$ Hz, 1H), 2.07−2.12 (m, 1H), 2.20−2.27 (m, 1H), 4.51 (d, $J = 6.8$ Hz, 1H), 5.22 (s, 1H), 5.37 (s, 1H); MS (*m*/*z*) 206 (M^+, 1), 173 (100), 145 (20), 73 (75). Anal. Calcd for $C_{12}H_{18}OSi$: C, 69.84; H, 8.79. Found: C, 69.54; H, 8.88.

[1*R*-[1α(*R),3a*β*,4α(1*S**,3S*,5S*),7aα]]-4-[[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-methylenebicyclo[3.1.0]-hexan-1-yl]ethynyl]octahydro-7a-methyl-1-[1,5,5-trimethyl-5-[(trimethylsilyl)oxy)pentyl]-1*H*-inden-4-ol (25).** A solution of 1.104 g (2.97 mmol) of acetylene **22** in 40 mL of THF at −30 °C was treated with 1.86 mL of an *n*-BuLi solution (1.6 M in hexane, 2.97 mmol) and then stirred at room temperature for 20 min. A solution of 0.950 g (2.70 mmol) of Grundmann ketone **6** in 5 mL of THF was added via syringe, and the resulting mixture was stirred at rt for 30 min. The reaction was quenched by the addition of 40 mL of H_2O, and the mixture was then extracted with ether. The extracts were combined, washed with water, and dried. The crude product was chromatographed on a silica gel, eluting with hexane−ether (99:1), to give 0.132 g of unreacted **6**. Further elution with hexane−ether (98:2) gave 1.742 g (89%) of **25** as a colorless oil: $[\alpha]^{25}_D = -49.6°$ (*c* 1.1, EtOH); UV λ_{max} (EtOH) 215 nm (ϵ = 18 580), 247 (260), 253 (380), 259 (520), 264 (580), 270 (430); IR ($CHCl_3$) 3590, 2230, 1660, 838 cm^{-1}; ^1H NMR δ 0.11 (s, 9H), 0.72 (t, $J = 5$ Hz, 1H), 0.90 (s, 3H), 0.91 (d, $J = 6.5$ Hz, 3H), 1.07 (s, 6H), 1.20 (s, 9H), 4.20 (brt, 1H), 5.30 (s, 1H), 5.32 (s, 1H), 7.3−7.45 (m, 6H), 7.65−7,70 (m, 4H); MS (*m*/*z*) 724 (M^+, 1), 667 (M − C_4H_9, 1), 315 (30), 237 (15), 199 (40), 131 (100); HRMS for $C_{46}H_{68}O_3Si_2$ calcd 724.4707, found 724.4722. Anal. Calcd for $C_{46}H_{68}O_3Si_2$: C, 76.19; H, 9.45. Found: C, 75.99; H, 9.37.

[1*R*-[1α(*R),3a*β*,4α(1*S**,3*S**,5*S**), 7aα]]-1-[1,5-Dimethyl-5-[(trimethylsilyl)oxy]hexyl]-4-[(3-hydroxy-2-methylenebicyclo[3.1.0]hexan-1-yl)ethynyl]octahydro-7a-methyl-1*H*-inden-4-ol (27) via Hydroxylation of 26.** To a suspension of 0.0707 g (0.64 mmol) of SeO_2 in 30 mL of dry CH_2Cl_2 was added 2.124 mL of a *t*-BuOOH solution (3.0 M in 2,2,4-trimethylpentane, 6.37 mmol), and the resulting mixture was stirred at rt for 1 h, and cooled to 0 °C and then 1.0 g (2.12 mmol) of olefin **26** in in 5 mL of CH_2Cl_2 was added. The reaction mixture was kept at 4 °C for 20 h whereupon 30 mL of 20% aqueous $Na_2S_2O_3$ was added. The mixture was stirred vigorously at rt for 0.5 h. The phases were separated, and the aqueous solution was extracted with ether. The organic extracts were combined, dried, and concentrated *in vacuo*. The residue was dried under high vacuum for 2 h, then dissolved in 40 mL of dry THF, and cooled to −50 °C. A lithium triethylborohydride solution (3.19 mL, 1 M in THF) was added dropwise over 5 min. The solution was then allowed to warm up to 0 °C and quenched by the addition of 30 mL of H_2O. The mixture was extracted with ether. The crude product was purified by silica gel chromatography, eluting with hexane−EtOAc (10:1), to give 0.827 g (80%) of **27**.

[1*R*-[1α(*R),3a*β*,4α(1*S**,3*S**,5*S**),7aα]]-4-[[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-methylenebicyclo[3.1.0]-hexan-1-yl]ethynyl]octahydro-7a-methyl-1-[1,5,5-trimethyl-5-[(trimethylsilyl)oxy]penthyl]-1*H*-inden-4-ol (25) from 27**. A solution of 0.146 g (0.3 mmol) of alcohol **27**, 0.041 g (0.6 mmol) of imidazole, 0.124 g (0.45 mmol) of *t*-$BuPh_2SiCl$, and 8 mL of CH_2Cl_2 was stirred at rt for 1 h. Then 20 mL of H_2O was added, and the mixture was extracted with hexane. The crude product was purified by silica gel chromatography, eluting with hexane−EtOAc (20:1), to give 0.190 g (88%) of **25** as a colorless oil.

Analytical and spectral data of **25** obtained in this manner were identical with those recorded for the material obtained by the coupling of **6** with **22** as described above.

[1*R*-[1α(*R),3a*β*,4α[(*E*)-(1*S**,3*S**,5*S**)],7aα]]-1-[1,5-Dimethyl-5-[(trimethylsilyl)oxy]hexyl]-4-[2-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-methylenebicyclo[3.1.0]-hexan-1-yl]ethenyl]octahydro-7a-methyl-1*H*-inden-4-ol (28).** A solution of 0.730 g (1.01 mmol) of acetylene **25** , 0.16 mL of a MeONa solution (25% in MeOH), 4 mL of a $LiAlH_4$

solution (1 M in THF), and 20 mL of THF was refluxed for 1h. The mixture was cooled and then quenched by the addition of 50 mL of saturated aqueous NH_4Cl. The mixture was extracted with ether, and the organic extract was washed with brine and then dried. The crude product was purified by chromatography on silica gel, eluting with hexane−ether (98:2), to give 0.648 g (88%) of **28** as a colorless oil: $[\alpha]^{25}_D = -5.0°$ (*c* 0.98, EtOH); UV λ_{max} (EtOH) 220 (ϵ = 25 000), 247 (390), 253 (480), 259 (645), 264 (690), 271 (515); IR ($CHCl_3$) 3600, 1652, 840 cm^{-1}; ^1H NMR δ 0.10 (s, 9H), 0.53 (brt, 1H), 0.88 (d, J = 6.4 Hz, 3H), 0.94 (s, 3H), 1.08 (s, 9H), 1.20 (s, 6H), 4.30 (t, J = 7.5 Hz, 1H), 4.95 (s, 1H), 5.24 (s, 1H), 5.37 (d, J = 15.5 Hz. 1H), 6.00 (d, J = 15.5 Hz, 1H), 7.3−7.5 (m, 6H), 7.6−7.7 (m, 4H); MS (*m*/*z*) 726 (M^+, 1), 711 (M − Me, 1), 669 (4), 199 (100), 131 (81); HRMS for $C_{46}H_{70}O_3Si_2$ calcd 726.4864, found 726.4857. Anal. Calcd for $C_{46}H_{70}O_3Si_2$: C, 75.97; H, 9.70. Found: C, 76.26; H, 9.97.

[1*R*-[1α(*R),3a*β*,4α[(*E*)-(1*S**,3*S**,5*S**)],7aα]]-Octahydro-4-hydroxy-4-[2-[(3-hydroxy-2-methylenebicyclo[3.1.0]-hexan-1-yl)ethenyl]-α,α,ϵ,7a-tetramethyl-1*H*-indene-pentanol (29).** A solution of 0.541 g (0.75 mmol) of **28**, 2.26 mL of tetrabutylammonium fluoride solution (1 M in THF, 2.26 mmol), and 8 mL of THF was stirred at rt for 16 h. The mixture was diluted with 50 mL of EtOAc and then washed 3 × 20 mL with water. The crude product was purified by chromatography on silica gel, eluting with CH_2Cl_2−ether (98:2), to give 0.307 g (99%) of **30** as a foam; $[\alpha]^{25}_D = +70.2°$ (*c* 0.88, EtOH); IR ($CHCl_3$) 3605, 1652 cm^{-1}; ^1H NMR δ 0.71 (t, J = 5.7 Hz, 1H), 0.92 (d, J = 6.5 Hz, 3H), 0.95 (s, 3H), 4.25 (q, J = 8.1 Hz, 1H, −CH−O−), 4.96 (d, J = 2.1 Hz, 1H), 5.08 (d, J = 2.0 Hz, 1H), 5.43 (d, J = 15.6 Hz, 1H), 5.97 (d, J = 15.6 Hz, 1H). MS (*m*/*z*) 416 (M^+, 1), 398 (M − 18, 3), 380 (M-32, 3), 355 (5), 139 (40), 55 (78), 28 (100); HRMS for $C_{27}H_{44}O_3$ calcd 416.3290, found 416.3313. Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.84; H, 10.64. Found: C, 77.77; H, 10.64.

1,25-Dihydroxycholecalciferol (1). A solution of 0.140 g (0.34 mmol) of **29**, 0.010 g of *p*-TsOH, and 25 mL of dioxane−H_2O (3:1) was stirred at 75 °C for 4 h. The cooled solution was extracted with EtOAc. The organic extracts were combined, washed successively with water and aqueous $NaHCO_3$, and then dried. The crude product was purified by silica gel chromatography, eluting with CH_2Cl_2−MeOH (96:4), to afford 0.105 g (75%) of a 5,6-*cis*/*trans* mixture of 1,25-$(OH)_2D_3$ which was subsequently irradiated for 1 h using a 450 W mercury lamp (uranium filter) in 70 mL of *tert*-butyl methyl ether containing 0.010 g of 9-acetoxyanthracene. The solvent was then evaporated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with CH_2Cl_2−MeOH (96:4), to give 0.100 g (71%) of 1,25-$(OH)_2D_3$ (**1**), mp 118−119 °C (methyl formate); $[\alpha]^{25}_D = +48°$ (*c* 0.5, EtOH); UV λ_{max} (EtOH) 210 nm (ϵ = 15 980), 263 (16 780); IR ($CHCl_3$) 1645, 1628 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 0.54 (s, 3H), 0.93 (d, J = 6.4 Hz, 3H), 1.20 (s, 6H), 4.19 (brs, 1H), 4.42 (brs, 1H), 4.97 (s, 1H), 5.33 (s, 1H), 6.04 (d, J = 11.0 Hz, 1H), 6.35 (d, J = 11.0 Hz, 1H); MS (*m*/*z*) 416 (M^+, 1), 398 (M − 18, 51), 380 ((M − 2 × 18, 76), 362 (M − 3 × 18, 22), 347 (10), 269 (14), 251 (28), 105 (59), 55 (72), 41 (100); HRMS for $C_{27}H_{44}O_3$ calcd 416.3296, found 416.3286. Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.84; H, 10.65. Found: C, 77.64; H, 10.67.

[1*R*-[1α(*R),3a*β*,4α(1*R**,5*R**),7aα]]-1-[1,5-Dimethyl-5-[(trimethylsilyl)oxy]hexyl]octahydro-7a-methyl-4-[(2-methylenebicyclo[3.1.0]hexan-1-yl)ethynyl]-1*H*-inden-4-ol (26).** A total of 9.30 mL (14.9 mmol) of an *n*-BuLi solution (1.6 M in hexane) was added at 0 °C to a solution of 2.36 g (12.4 mmol) of **19** in 70 mL of THF. The solution was then stirred at 50 °C for 15 min before being cooled to −30 °C, whereupon a solution of 3.97 g (11.3 mmol) of **6** in 10 mL of THF was added. The reaction mixture was stirred at −15 °C for 20 min and at 0 °C for 30 min and then quenched by the addition of 100 mL of H_2O. The mixture was extracted with ether, and the extracts were combined and dried. The crude product was purified by silica gel chromatography, eluting with hexane−EtOAc (10:1), to give 4.14 g (78%) of **26** as a colorless oil: $[\alpha]^{25}_D = -9.2°$ (*c* 1.0, EtOH); IR ($CHCl_3$) 3595, 2225, 1650 cm^{-1}; ^1H NMR δ 0.13 (s, 9H), 0.89 (d, J = 4.3 Hz, 3H), 0.90 (s, 3H), 1.01 (t, J = 4.5 Hz, 1H), 1.20 (s, 6H), 4.87 (s, 1H), 5.11 (s, 1H); MS (*m*/*z*) 131 (100), 73 (40), 28 (63). Anal. Calcd for $C_{30}H_{50}O_2Si$: C, 76.53; H, 10.70. Found: C, 76.56; H, 10.86.

[1*R*-[1α(*R),3a*β*,4α[(*E*)-(1*S**,5*R**)],7aα]]-1-[1,5-Dimethyl-5-[(trimethylsilyl)oxy)hexyl]octahydro-7a-methyl-4-[2-[2-methylenebicyclo-[3.1.0]hexan-1-yl)ethenyl]-1*H*-inden-4-ol (30).** A 1 M $LiAlH_4$ in THF solution (24.3 mL) was added to 45 mL of THF followed by 2.75 mL of MeONa (4.37 M in MeOH, 12.0 mmol). The mixture was stirred at rt for 10 min and cooled to 0 °C, and then 3.82 g (8.12 mmol) of **26** in 8 mL of THF was added over 10 min. The reaction mixture was stirred at rt for 15 min and then quenched by the careful addition of 50 mL of H_2O. The mixture was extracted with 2 × 30 mL of ether, and the combined extracts were dried. The crude product was purified by silica gel chromatography, eluting with hexane−EtOAc (10:1), to afford 2.99 g (78%) of **30**: $[\alpha]^{25}_D = +50.9°$ (*c* 0.9, EtOH); = IR ($CHCl_3$) 3595, 1642 cm^{-1}; ^1H NMR δ 0.00 (s, 9H), 0.71 (t, J = 4.5 Hz, 1H), 0.81 (d, J = 6.5 Hz, 3H), 0.85 (s, 3H), 1.01 (s, 6H), 4.64 (s, 1H), 4.70 (s, 1H), 5.31 (d, J = 15.6 Hz, 1H), 5.85 (d, J = 15.6 Hz, 1H); MS (*m*/*z*) 131 (100); HRMS for $C_{30}H_{52}O_2Si$ calcd 472.3737, found 472.3744. Anal. Calcd for $C_{30}H_{52}O_2Si$: C, 76.21; H, 11.09. Found: C, 76.11; H, 11.26.

[1*R*-[1α(*R),3a*β*,4α[(*E*)-(1*S**,5*R**)],7aα]]-Octahydro-4-hydroxy-α,α,ϵ,7a-tetramethyl-4-[2-(2-methylenebicyclo-[3.1.0]hexan-1-yl)ethenyl]-1*H*-indene-pentanol (31).** A solution of 1.95 g (4.13 mmol) of **30**, 8.24 mL of an *n*-Bu_4NF solution (1 M in THF) and 20 mL of THF was stirred at rt for 3 h. Then 20 mL of H_2O was added, and the mixture was extracted with 2 × 20 mL of ether. The extracts were combined and dried. The crude product was purified by silica gel chromatography, eluting with hexane−EtOAc (4:1), to give 1.62 g (98%) of **31** as a colorless oil: IR ($CHCl_3$) 3606, 1645 cm^{-1}; ^1H NMR δ 0.81 (t, J = 4.5 Hz, 1H), 0.92 (d, J = 6.2 Hz, 3H), 0.95 (s, 3H), 1.21 (s, 6H), 4.75 (s, 1H), 4.80 (s, 1H), 5.41 (d, J = 15.6 Hz, 1H), 5.96 (d, J = 15.6 Hz, 1H); MS (*m*/*z*) 41 (100). HRMS for $C_{27}H_{44}O_2$ calcd 400.3341, found 400.3344. Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.09. Found: C, 80.87; H, 11.36.

25-Hydroxycholecalciferol (32). A solution of 1.23 g (3.07 mmol) of **31**, 0.231 g (0.92 mmol) of pyridinium *p*-toluenesulfonate, 24 mL of acetonitrile, and 12 mL of H_2O was stirred vigorously at 50 °C for 2.5 h. Then 20 mL of saturated aqueous $NaHCO_3$ was added and the mixture extracted with ether. The extracts were combined and dried and solvents were removed under reduced pressure at 30 °C. The residue was dissolved in a mixture of hexane−EtOAc (2:1) and filtered through a 1 cm pad of silica gel, eluting with the same solvent mixture. The filtrates were evaporated at 30 °C under reduced pressure, and the residue was subsequently dissolved in 20 mL of *t*-BuOMe. The solution was irradiated under argon with a 450 W mercury lamp, through a uranium filter, in the presence of 0.181 g (0.77 mmol) of 9-acetoxyanthracene for 2 h. The solvent was then evaporated under reduced pressure at 30 °C, and the residue was purified by silica gel chromatography, eluting with hexane−EtOAc (2:1), to give 0.8 g (65%) of 25-hydroxycholecalciferol (**32**) as a white solid. The analytical sample was prepared by crystallization from methyl formate, mp 96−106 °C (lit.[32] mp 95−100 °C, acetone), $[\alpha]^{25}_D = +88.1°$ (*c* 0.5, EtOH).

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(32) Halkes, S. J.; van Vliet, N. P. *Rec.* **1969**, *88*, 1080.